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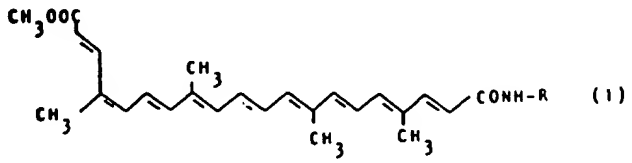
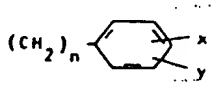
(54) New derivatives of the 9-cis-6,6'-diapo-psi,psi-carotenedioic acid, preparation thereof and pharmaceutical compositions containing same.

(57) The invention provides new derivatives of the 9-cis-6,6'-diapo-ψ,ψ-carotenedioic acid of general formula



(I)

wherein R is a radical selected from the group comprising



(wherein n = 0,1,2 and x, y, the same of different are H, halogen, alkoxy, hydroxy, alkyl or trifluoromethyl radical); 2,3-pyridyl; 4-pyridyl; 2,3-pyridyl-methyl; 3-pyridyl-methyl.

The compounds of the formula (I) can be prepared from the corresponding acid by directly reacting an amine of the formula $R\text{-}NH_2$ (wherein R has the proviously specified

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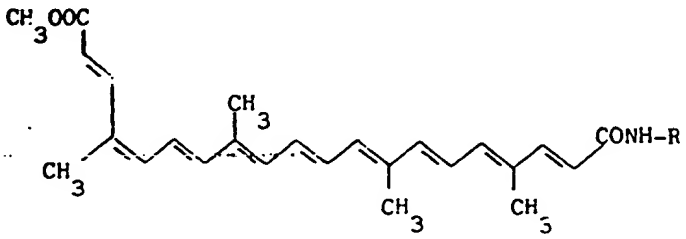
meanings) in an aprotic solvent in the presence of an activator for the carboxylic group, or by previously transforming the above mentioned acid into the corresponding acid chloride or into the corresponding mixed anhydride and then carrying out the reaction with the amine $R\text{-}NH_2$. The compounds of formula (I) are used in pharmaceutical compositions useful in the therapeutic prevention of diseases.

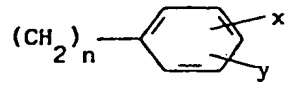
The present invention provides to new derivatives of the 9-cis-6,6'-diapo-ψψ-carotenedioic acid, their preparation and the pharmaceutical compositions containing them.

More particularly, the present invention provides new derivatives the 9-cis-6,6'-diapo-ψψ-carotenedioic acid of the general formula (I)



(I)

wherein R is a radical selected from the group comprising



(wherein n=0,1,2 and x,y, the same or different, are H, halogen, alkoxy, hydroxy, alkyl or trifluoromethyl radical);

2,3-pyridyl; 4-pyridyl;

2,3-pyridyl-methyl; 3-pyridyl-methyl.

More specifically, the present invention provides the following compounds comprised in the general formula (I)

1) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, benzylamide monomethyl ester;
2) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, 3,4-dimethoxy-benzylamide monomethyl ester;
3) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, phenethylamide monomethylester;
4) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, 3,4-dimethoxyphenethylamide monomethyl ester;

5) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, anilide monomethylester;

6) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, p-methoxyanilide monomethylester;

7) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, p-chloroanilide monomethylester;

8) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, 3,4-dichloroanilide monomethylester;

9) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, 2,5-dimethoxyanilide monomethylester;

10) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, 2,3-dimethylanilide monomethylester;

11) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, p-hydroxyanilide monomethylester;

12) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, m-hydroxyanilide monomethylester;

13) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, o-hydroxyanilide monomethylester;

14) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, m-fluoroanilide monomethylester;

15) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, p-fluoroanilide monomethylester;

16) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, o-fluoroanilide monomethylester;

17) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, 4-pyridylamide monomethylester;

18) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, 3-pyridylmethylamide monomethylester;

19) 9-cis-6,6'-diapo-ψψ-carotenedioic acid, 3-trifluoromethylanilide monomethylester.

The new products of this invention are endowed with antiproliferating activity.

As far as this activity is concerned, compound 18, tested "in vivo", has proved particularly useful.

By carrying out the test as indicated hereinbelow, the average survival time has been evaluated for mice (strain CD_2F_1) treated, or not, with compound 18.

Lymphocytic leukaemia was induced in the mice to be tested (i.p. inoculum; number of injected cells 10^6; tissue: ascitic fluid).

Three groups each consisting of 6 female mice have been treated. The compound has been injected using as vehicle a physiological solution with TWEEN-80 at dosages of 200, 100 and 50 mg/kg respectively.

The drug has been injected once a day for 9 days from the day immediately after the inoculum.

The used controls were 32.

The mortality of both treated mice and controls calculated on the treatment days is summarized in the following table:

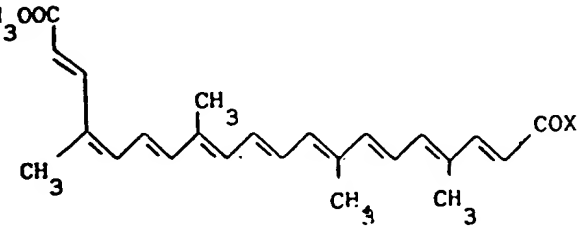
Days	N° of dead animals after treatment with			N° of dead controls
	200 mg/kg	100 mg/kg	50 mg/kg	
VI				
VII				
VIII	1			8
IX				15
X				5
XI			3	4
XII	3	4	3	
XIII	2	2		
XIV				

Therefore, the average survival times are as follows:

Dosage	survival time (days)
200 mg	12.3
100 mg	12.4
50 mg	11.7
control	9.1

The percentage ratio (T/C) between the average survival time of the treated animals and that one of the controls is 135, 136, 128% respectively for dosages of 200, 100 and 50 mg/kg respectively.

The new compounds of the present invention can be prepared by reacting the compound of formula (II)



(II)

wherein X is -OH, Cl or the group O-CO-O-R_1, R_1 being CH_3, C_2H_5, C_4H_7 or CH_2CCl_3, is reacted with a compound R-NH_2 (wherein R has the previously specified meanings).

When X is -OH the reaction may be carried out in an aprotic polar solvent selected from $CHCl_3$, CH_2Cl, tetrahydrofurane and dimethylsulfoxide, in the presence of an activator for the carboxylic group, such as for instance bicyclohexylcarbodiimide, at a temperature comprised between -10 °C and +50 °C.

When X is Cl, the acid chloride may be prepared by reacting the compound wherein X=OH with PCl_3 in a chlorinated solvent selected from $CHCl_3$, CH_2-Cl_2 and Cl_2-CH-CH-Cl_2 and then allowing the thus

formed acid chloride to react in situ with $R-NH_2$ in excess.

When X is $O-C-O-R_1$ the acid may be reacted in the presence of an aprotic solvent selected from CH_2Cl_2, dioxane, tetrahydrofurane, diglyme, dimethylsulfoxide, dimethylformamide, first with an organic base selected from triethylamine, diisopropylethylamine and dimethylaniline and thereafter with a derivative of the chlorocarbonic acid of the general formula $Cl-CO-OR_1$ (wherein R_1 has the above specified meaning), at temperatures comprised between -20 °C and 0 °C.

The thus obtained mixed anhydride may be then allowed to react, in the same solvent where it has been formed, with 2 molar eq. of the amine $R-NH_2$, at temperatures comprised between 10 °C and 80 °C to yield the desidered compounds.

The new compounds of the present invention are crystalline substances endowed with well defined physico-chemical characteristics and colour generally varying from orange to dark red.

For the application in the pharmaceutical field, the compounds of the invention can be made up in a suitable form for topic and systemic use (oral and injectable administration, suppositories).

To this purpose the compounds of the invention can be formulated as compositions containing, besides the active substance, the generally used solvents, excipients, adjuvants, stabilizers and vehicles.

The dosages of active substance are comprised between 1 and 500 mg.

The following examples are given to illustrate the invention without limiting it in any way.

Example 1

500 mg of monomethylester of the 9-cis-6,6'-diapo-ψψ-carotene-

dioic acid and 136 mg of benzylamine are suspended in 10 ml of CH_2Cl_2 and added with 265 mg of bicyclohexylcarbodiimide.

The thus obtained solution is left to stand for 15 h at room temperature and thereafter it is diluted with 40 ml CH_2Cl_2. The bicyclohexylcarbourea is filtered off and then the solution is washed with diluted HCl and water, dried on Na_2SO_4 and evaporated to dryness. The residue is analysed by chromatography on silica gel using as eluent CH_2Cl_2 containing 0.5% methanol.

By crystallization from acetone, 300 mg of 9-cis-6,6'-diapo-ψψ--carotenedioic acid, benzylamide monomethylester (compound 1) are obtained.

m.p. = 173-175 °C; M^+ 469.

The analysis for $C_{31}H_{35}NO_3$ gives the following results:

	C	H	N
calculated (%)	79.28	7.51	2.98
found (%)	78.53	7.47	2.86

λ_{max}^{MeOH} 494 mμ, 464 mμ

By working as above described, there are prepared the following compounds:

- compound 2

  9-cis-6,6'-diapo-ψψ-carotenedioic acid, 3,4-dimethoxy-benzyl-amide monomethylester.

  m.p. = 193-195 °C ($CHCl_3$/acetone) M^+ 543.

  The analysis for $C_{34}H_{41}NO_5$ gives the following results:

	C	H	N
calculated (%)	75.11	7.60	2.58
found (%)	74.34	7.37	2.65

  λ_{max}^{MeOH} 488 mμ, 459 mμ

- compound 3

9-cis-6,6'-diapo-ψψ-carotenedioic acid, phenethylamide monomethylester.

m.p. = 192-194 °C (dioxane) M^+ 497

The analysis for $C_{33}H_{39}NO_3$ gives the following results:

	C	H	N
calculated (%)	79.64	7.90	7.81
found (%)	79.13	7.53	2.69

λ_{max}^{MeOH} 488 mμ, 459 mμ

- compound 4

9-cis-6,6'-diapo-ψψ-carotenedioic acid, 3,4-dimethoxyphenethylamide monomethylester.

m.p. = 200-201 °C ($CHCl_3$/acetone) M^+ 557

The analysis for $C_{35}H_{43}NO_5$ gives the following results:

	C	H	N
calculated (%)	75.37	7.77	2.51
found (%)	75.00	7.42	2.42

λ_{max}^{MeOH} 488 mμ, 459 mμ

Example 2.

5 g of finely grounded 9-cis-6,6'-diapo-ψψ-carotenedioic acid, monomethylester are suspended in 250 ml of CH_2Cl_2 cooled to 0 °C and treated with 1.17 g of PCl_3.

After 15 h at room temperature the mixture is again cooled to 0 °C and 4.8 g of aniline are added. After 2 h at room temperature the reaction mixture is poured into 500 g of ice containing 30 ml of concentrated HCl.

The organic layer is separated, washed with water, with a $NaHCO_3$

solution and again with water to neutral reaction and finally is dried on Na_2SO_4 and concentrated to dryness.

The residue is analysed by chromatography on silica gel.

As eluent CH_2Cl_2 is first used and then CH_2Cl_2 containing 1% methanol. Using this last mixture unitary fractions are obtained which by evaporation and crystallization from acetone yield 1.6 g of 9-cis-6,6'diapo-ψψ-carotenedioic acid, anilide monomethylester (compound 5).

m.p. 173-175 °C; M^+ 469.

The analysis for $C_{31}H_{35}NO_3$ gives the following results:

	C	H	N
calculated (%)	79.28	7.51	2.98
found (%)	78.33	7.37	2.86

λ_{max}^{MeOH} 494 mμ, 464 mμ

Example 3

5 g of 9-cis-6,6'-diapo-ψψ-carotenedioic acid, monomethylester are suspended in 50 ml dioxane and treated with 1.5 g triethylamine. The thus obtained solution is cooled to +5 °C and added with 1.5 g of methylchloroformiate. The solution is stirred at room temperature for 1.5 h; thereafter 3.0 g of p-anisidine are added. After 24 h at room temperature the reaction is completed.

The solution is evaporated to dryness and the residue is treated with acetone/ether; the thus formed solid is filtered off, washed with ether and crystallized from acetone.

2.5 g of 9-cis-6,6'-diapo-ψψ-carotenedioic acid, p-methoxyanilide monomethylester (compound 6) are obtained.

m.p. = 177-179 °C, M^+ 499.

The analysis for $C_{32}H_{37}NO_4$ gives the following results:

	C	H	N
calculated (%)	76.92	7.46	2.80
found (%)	75.63	7.38	2.60

λ_{max}^{MeOH} 494 mμ, 464 mμ

By analogously working there are prepared the hereinbelow described compounds.

- compound 7

9-cis-6,6'-diapo-ψψ-carotenedioic acid, p-chloroanilide monomethylester.

m.p. = 178-180 °C (acetone); M^+ 505, 503.

The analysis for $C_{31}H_{34}ClNO_3$ gives the following results:

	C	H	N
calculated (%)	78.87	6.80	2.78
found (%)	72.19	6.62	2.58

λ_{max}^{MeOH} 494 mμ, 464 mμ

- compound 8

9-cis-6,6'-diapo-ψψ-carotenedioic acid, 3,4-dichloroanilide monomethylester.

m.p. = 170-172 °C (acetone); M^+ 539, 537

The analysis for $C_{31}H_{33}ClNO_3$ gives the following results:

	C	H	N
calculated (%)	69.14	6.18	2.60
found (%)	68.56	5.97	2.45

λ_{max}^{MeOH} 487 mμ, 459 mμ

- compound 9

9-cis-6,6'-diapo-ψψ-carotenedioic acid, 2,5-dimethoxyanilide

monomethylester.

m.p. = 152-155 °C (acetone); M^+ 529

The analysis for $C_{33}H_{39}NO_5$ gives the following results:

	C	H	N
calculated (%)	74.83	7.42	2.64
found (%)	74.11	7.76	2.69

λ_{max}^{MeOH} 494 mμ, 464 mμ

- compound 10

9-cis-6,6'-diapo-ψψ-carotenedioic acid, 2,3-dimethylanilide monomethylester.

m.p. = 187-188 °C (acetone), M^+ 497

The analysis for $C_{33}H_{39}NO_3$ gives the following results:

	C	H	N
calculated (%)	79.64	7.90	2.81
found (%)	78.56	7.71	2.63

λ_{max}^{MeOH} 488 mμ, 460 mμ

- compound 11

9-cis-6,6'-diapo-ψψ-carotenedioic acid, p-hydroxyanilide monomethylester.

m.p. = 210-211 °C (dioxane); M^+ 485

The analysis for $C_{31}H_{35}NO_4$ gives the following results:

	C	H	N
calculated (%)	76.67	7.26	2.88
found (%)	75.05	7.15	2.65

λ_{max}^{MeOH} 494 mμ, 464 mμ

- compound 12

9-cis-6,6'-diapo-ψψ-carotenedioic acid, m-hydroxyanilide monomethylester.

m.p. = 149-152 °C (acetone); M^+ 485

The analysis for $C_{31}H_{35}NO_4$ gives the following results:

	C	H	N
calculated (%)	76.67	7.26	2.88
found (%)	75.97	7.43	2.80

λ_{max}^{MeOH} 490 mμ, 462 mμ

- compound 13

9-cis-6,6'-diapo-ψψ-carotenedioic acid, o-hydroxyanilide monomethylester.

m.p. = 208-210 °C (acetone); M^+ 485

The analysis for $C_{31}H_{35}NO_4$ gives the following results:

	C	H	N
calculated (%)	76.67	7.26	2.88
found (%)	75.68	7.66	2.86

λ_{max}^{MeOH} 492 mμ, 464 mμ

- compound 14

9-cis-6,6'-diapo-ψψ-carotenedioic acid, m-fluoroanilide monomethylester.

m.p. = 171-172 °C (acetone); M^+ 487

The analysis for $C_{31}H_{34}FNO_3$ gives the following results:

	C	H	N
calculated (%)	76.36	7.03	2.87
found (%)	75.52	6.98	2.79

λ_{max}^{MeOH} 494 mμ, 462 mμ

- compound 15

9-cis-6,6'-diapo-ψψ-carotenedioic acid, p-fluoroanilide mono-methylester.

m.p. = 170-171 °C (acetone); M^+ 187

The analysis for $C_{31}H_{34}FNO_3$ gives the following results:

	C	H	N
calculated (%)	76.36	7.03	2.87
found (%)	76.25	6.91	2.56

λ_{max}^{MeOH} 490 mμ, 462 mμ

- compound 16

9-cis-6,6'-diapo-ψψ-carotenedioic acid, o-fluoroanilide mono-methylester.

m.p. = 182-183 °C (acetone); M^+ 187

The analysis for $C_{31}H_{34}FNO_3$ gives the following results:

	C	H	N
calculated (%)	76.36	7.03	2.87
found (%)	76.13	6.90	2.98

λ_{max}^{MeOH} 494 mμ, 462 mμ

- compound 17

9-cis-6,6'-diapo-ψψ-carotenedioic acid, 4-pyridylamide mono-methylester.

m.p. = 192-194 °C (acetone); M^+ 470

The analysis for $C_{30}H_{34}N_2O_3$ gives the following results:

	C	H	N
calculated (%)	76.56	7.28	5.95
found (%)	75.04	7.33	5.57

λ_{max}^{MeOH} 490 mμ, 468 mμ

- compound 18

9-cis-6,6'-diapo-ψψ-carotenedioic acid, 3-pyridylmethylamide monomethylester.

m.p. = 197-199 °C ($CHCl_3$/acetone); M^+ 484

The analysis for $C_{31}H_{36}N_2O_3$ gives the following results:

	C	H	N
calculated (%)	76.83	7.49	5.78
found (%)	76.84	7.26	5.78

λ_{max}^{MeOH} 489 mμ, 460 mμ

- compound 19

9-cis-6,6'-diapo-ψψ-carotenedioic acid, 3-trifluoromethylanilide monomethylester.

m.p. = 172-175 °C (acetone); M^+ 537

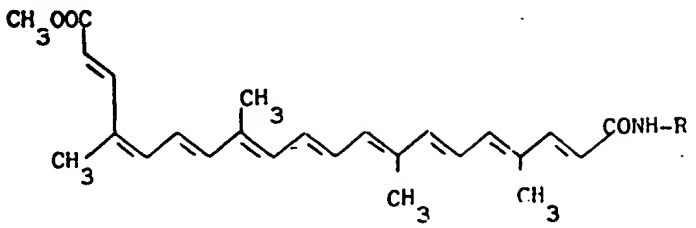
The analysis for $C_{32}H_{34}F_3O_3$ gives the following results:

	C	H	N
calculated (%)	71.49	6.37	2.61
found (%)	70.80	6.21	2.45

λ_{max}^{MeOH} 494 mμ, 462 mμ

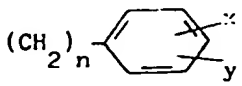
C l a i m s:

1. Derivatives of the 9-cis-6,6'-diapo-ψψ-carotenedioic acid of the general formula (I)



(I)

wherein R is a radical selected from the group comprising



(wherein n=0,1,2 and x,y, equal or different, are H, halogen, alkoxy, -OH, alkyl or trifluoromethyl radical);

2,3-pyridyl; 4-pyridyl;

2,3-pyridyl-methyl; 3-pyridyl-methyl.

2. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, benzylamide monomethylester.

3. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, 3,4-dimethoxy-benzylamide monomethylester.

4. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, phenethylamide monomethylester.

5. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, 3,4-dimethoxyphenethylamide monomethylester.

6. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, anilide monomethyl ester.

7. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, p-methoxyanilide monomethylester.

8. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, p-chloroanilide mono-

methylester.

9. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, 3,4-dichloroanilide monomethylester.

10. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, 2,5-dimethoxyanilide monomethylester.

11. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, 2,3-dimethylanilide monomethylester.

12. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, p-hydroxyanilide monomethylester.

13. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, m-hydroxyanilide monomethylester.

14. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, o-hydroxyanilide monomethylester.

15. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, m-fluoroanilide monomethylester.

16. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, p-fluoroanilide monomethylester.

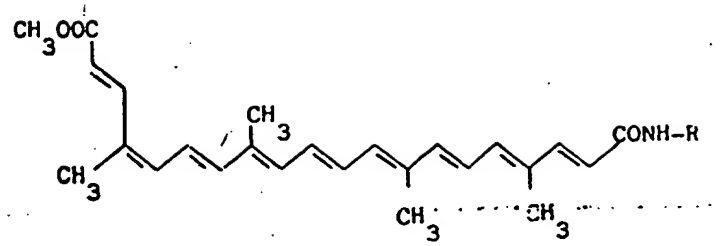
17. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, o-fluoroanilide monomethylester.

18. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, 4-pyridylmethylamide monomethylester.

19. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, 3-pyridylmethylamide monomethylester.

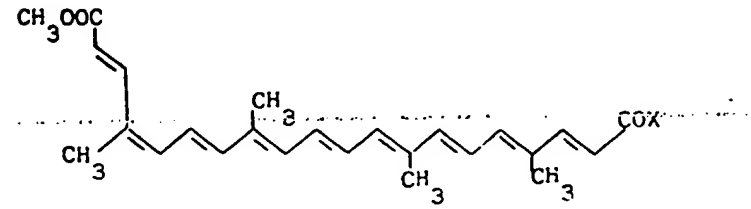
20. 9-cis-6,6'-Diapo-ψψ-carotenedioic acid, 3-trifluoromethylanilide monomethylester.

21. A process for the preparation of derivatives of the 9-cis-6,6'-diapo-ψψ-carotenedioic acid of the general formula (I)



(I)

characterized in that a compound of the formula



wherein X is -OH, Cl or the group O-CO-O-R_1, R_1 being CH_3, C_2H_5, C_4H_7 or CH_2CCl_3, is reacted with a compound R-NH_2 (wherein R has the above specified meanings).

22. A process according to claim 21, characterized in that when X=OH, the reaction is carried out in an aprotic solvent, in the presence of an activator for the carboxylic group, at a temperature comprised between -10 °C and +50 °C.

23. A process according to claim 22, characterized in that the aprotic solvent is selected from the class consisting of $CHCl_3$, CH_2Cl_2, tetrahydrofurane, dimethylsulfoxide.

24. A process according to claim 22, characterized in that the activator for the carboxylic group is bicyclohexylcarbodiimide.

25. A process according to claim 21, characterized in that when X=Cl, the acid chloride is prepared by reacting the compound wherein X=OH with PCl_3, in chlorinated solvent, and thereafter the obtained acid chloride in situ with R-NH_2.

26. A process according to claim 25, characterized in that the chlorinated solvent is selected from the class consisting of

$CHCl_3$, CH_2Cl_2, Cl_2-CH-CH-Cl_2.

27. A process according to claim 25, characterized in that the preparation of the acid chloride is carried out in the presence of $R-NH_2$ in excess.

28. A process according to claim 21, characterized in that when X is $O-C-O-R_1$, the compound wherein X=OH is reacted in the presence of an aprotic solvent, first with an organic base and thereafter, at a temperature comprised between -10 °C and 0 °C, with a derivative of the chlorocarbonic acid of the formula

$$Cl-\overset{\overset{O}{\|}}{C}-O-R_1$$

wherein R_1 has the previously specified meaning, the mixed anhydride being then allowed to react with $R-NH_2$ (wherein R has the meaning specified in claim 1) at a temperature comprised between 10° and 80 °C.

29. A process according to claim 28, characterized in that the aprotic solvent is selected from CH_2Cl_2, dioxane, tetrahydrofurane, diglyme, dimethylsulfoxide and dimethylformamide and the organic base is selected from diisopropylethylamine and dimethylaniline.

30. A process according to claim 28, characterized in that the reaction between the mixed anhydride and $R-NH_2$ occurs in the same solvent wherein the mixed anhydride has been formed and with 2 molar eq. of the amine.

31. Pharmaceutical compositions containing as active ingredient a compound of the general formula (I) together with pharmaceutically acceptable excipients and vehicles.

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 80107404.8

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
	GB - A - 1 254 771 (BP CHEMICALS) + Claims + --	1
	US - A - 4 024 151 (P.C. WADE, B.R. VOGT) + Claims + ----	1

CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

C 07 C 103/58
C 07 C 102/04
C 07 D 213/40
C 07 D 213/75
A 61 K 31/225
A 61 K 31/44

TECHNICAL FIELDS SEARCHED (Int. Cl.³)

C 07 C 103/00
C 07 D 213/00
C 07 C 102/00
A 61 K 31/00

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	16-02-1981	HOFBAUER

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